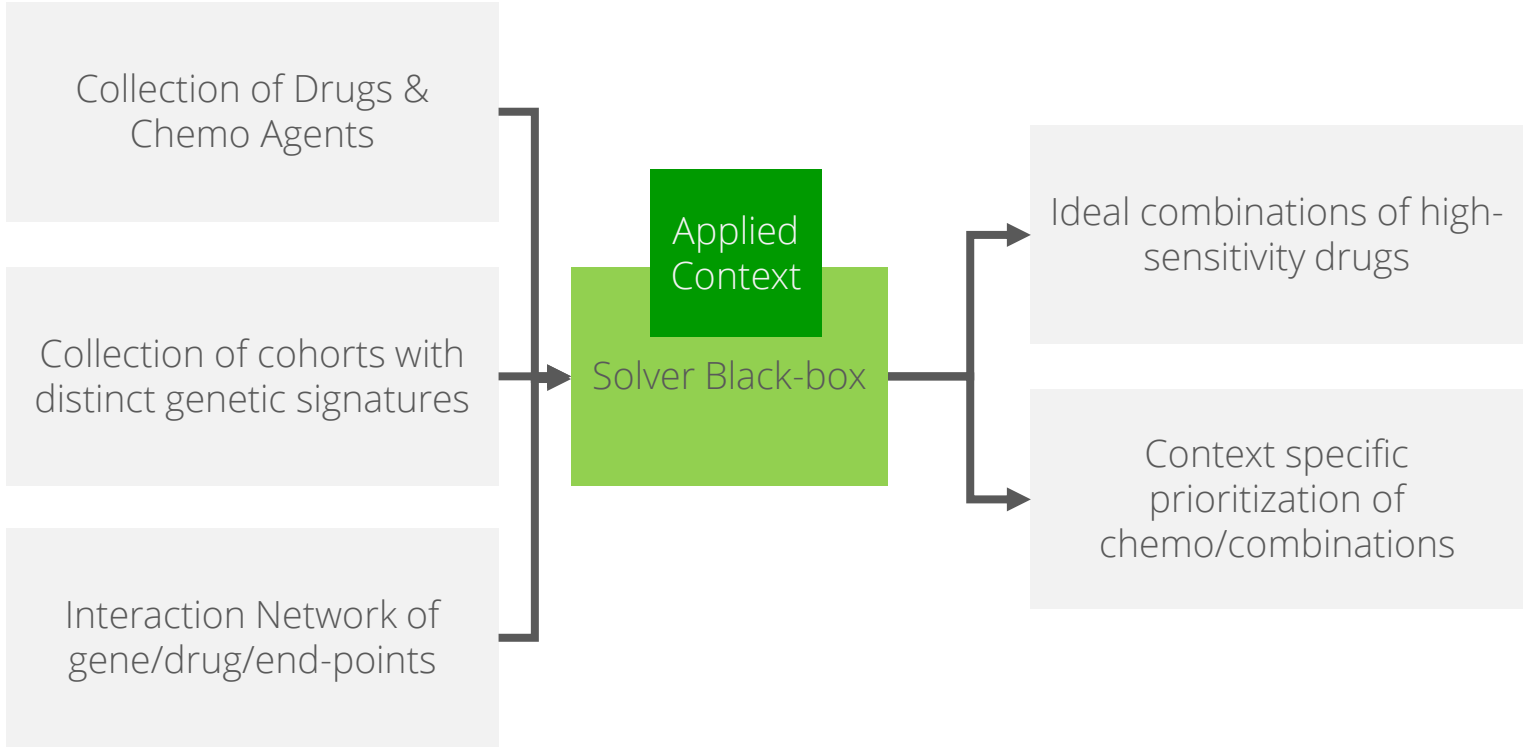
PROCESS FLOW - OUTLINE

DEFINING THE PROBLEM STATEMENT

MODEL DEFINITION & PARAMETERIZATION



Input Variables

Genes : Mutations, CNAs, Present/Absent
Drugs : Drug X Pathway mapping data
Network: Gene X Pathway mapping data

Output Variables

Drug Combinations : weightage for each combination

Parametric Variables

Context Vector: Gene + Pathway vector containing Desired output ranges.

SYSTEM INITIALIZATION

MATRIX NOTATION & BASIS FUNCTIONS

Defining the Network Interaction

Network interaction is defined as a bi-partite mapping of genes to the respective pathways. The weightage and sign determines the magnitude of effective impact and the direction of impact on the system.

$$N = \begin{bmatrix} P_1 & P_2 & \cdots & P_n \\ G_1 & 0.3 & 0.96 & \cdots \\ G_2 & -0.5 & \cdots & \cdots \\ \vdots & 0.2 & \ddots & \\ G_n & & & \end{bmatrix}$$

$$U = \begin{bmatrix} Indc_1 & Indc_2 & \cdots & Indc_n \\ G_1 & 0.03 & 0.76 & \cdots \\ G_2 & 0.05 & \cdots & \cdots \\ \vdots & 0.25 & \ddots & \\ G_n & & & \\ P_1 & & & \\ \vdots & & & \\ P_n & & & \end{bmatrix}$$

Defining the Indication Cohort

An indication is defined as the collection of mutations and copy-number alterations weighted by the frequency of occurrence. A vector notation is used to define the subset of mutations is the cohort or patient containing the sub-set of mutations within the indication.

$$S = \begin{bmatrix} Indc & \\ G_1 & 0.03 \\ G_2 & 0.05 \\ \vdots & 0.54 \\ G_n & \vdots \\ P_1 & \\ \vdots & \\ P_n & \end{bmatrix} \odot \begin{bmatrix} 1 \\ 1 \\ 0 \\ \vdots \\ \vdots \\ \vdots \\ \vdots \\ 1 \end{bmatrix}$$

Defining the Drug Interactions

A drug or chemo component causatively activates/inhibits a pathway or a gene, thus creating a cascading impact on pathways or gene. This action of drug/chemo element is captured in the simplified drug interaction function.

$$H = \begin{bmatrix} Drug_1 & Drug_2 & \cdots & Drug_n \\ T_1 & (0.5, Dir = 1) & (0.33, Ind = 2) & \cdots \\ T_2 & (-0.5, Dir = 1) & \cdots & \cdots \\ \vdots & (-0.25, Ind = 2) & \ddots & \\ T_n & & & \end{bmatrix}$$

$$ic = \frac{1}{(1 + \frac{D_{ix}}{K_i})}$$

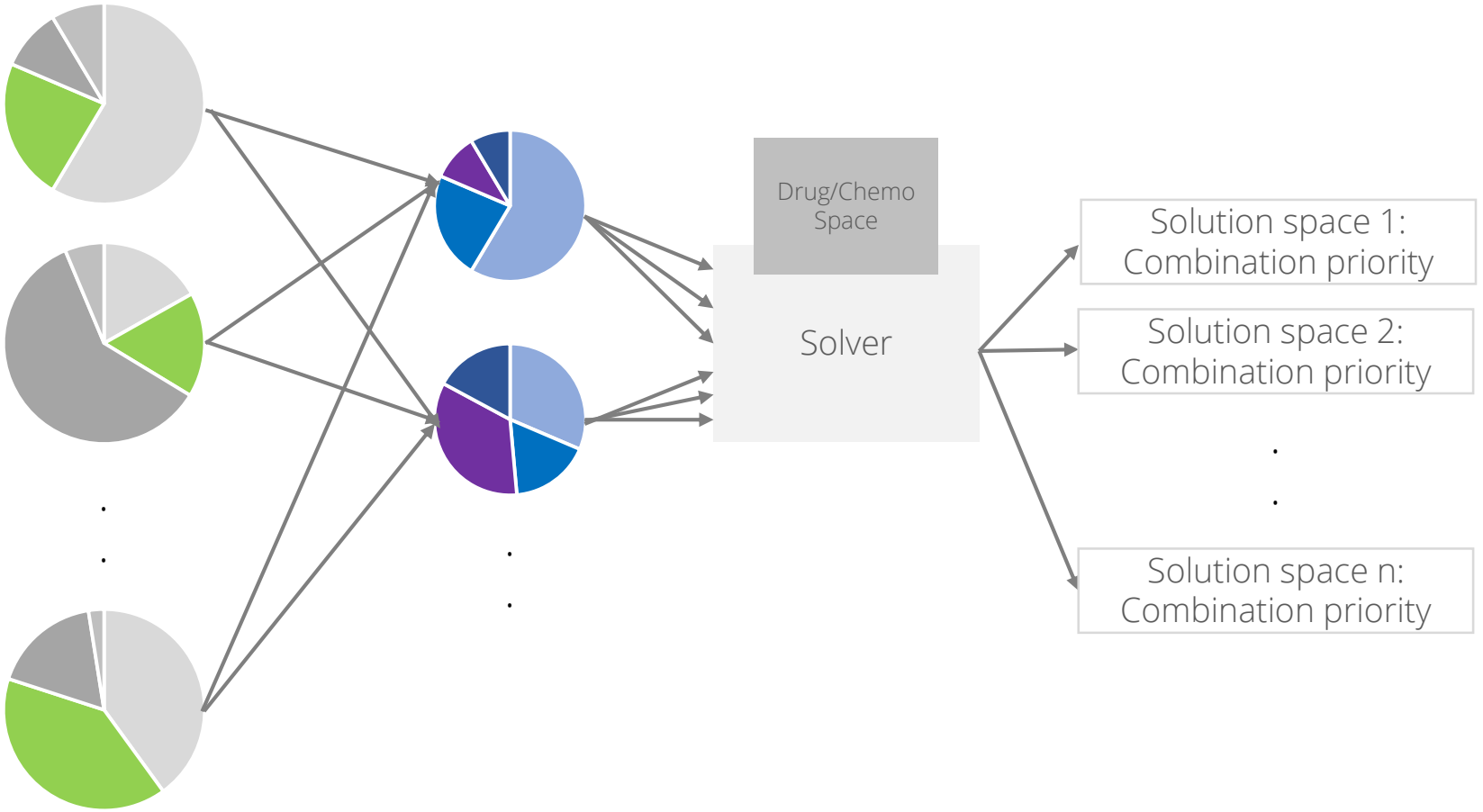
Defining the Initial Conditions

The starting point of the problem statement is define by initializing the vector with its respective pathway entries by magnitude/direction defined by a set of basis rules. These rules are defined to compliment each other for ease of computation during solution phase.

Mutation Rules : CNA+ = 0.5, CNA- = -0.75, MUT+ = 1.5 ...

Drug Rules : Rank Priority: 1/(1+Rank)

END-POINTS & CONTEXTS



Changing the context

changes the drug prioritization

A **cohort** is a the set of mutations subset of the indication defined as the input

A **context** / end-point is the objective Pathways/Biomarkers distribution we expect as a response to drugs/chemo

A **solution** space consists of drug combination priority which enables to achieve the expected end-point for each cohort

SOLVING THE SYSTEM

SINGULAR VALUE DECOMPOSITON

Step 1

Creating combinations of Drug/chemo elements

For each drug, a exhaustive n-group combination list (D) is created and anchored with the list of chemo drugs.

$$D = \sum_{j=1}^{N} C_j \sum_{k=1}^{M} {}^{M}H_k$$

A Drug-Drug-Interaction Matrix (DDIM) is computed on the fly where co-occurring pathways between drugs are updated linearly with values of interaction

Step 2

Simulating the interaction of Drug X Network

The effect of each drug and each combination on the pathways and genes in the network is computed sequentially for each cohort defined in the input set.

$$V_{(i,j)} = \sum_{i}^{N} D^{j}_{G_i} \cdot G^{I}_{w}$$

$$I = [V_{D_1,G..P}, V_{D_2,G..P} \cdots V_{D_n,G..P}]$$

$$I = \begin{bmatrix} Drug_1 & Drug_2 & \cdots & Drug_n \\ G_1 & -1.3 & 0.96 & \cdots \\ G_2 & 2.3 & \cdots & \cdots \\ \vdots & 0.32 & \ddots & \\ G_n & & & \end{bmatrix}$$

Step 3

Solving the system of linear equations

Once the drug X network computation is performed for each cohort for each drug combination set, the system is redefined to solve for the context vector (C) to obtain the weightage vector.

$$I \cdot w = C$$

$$w = ((I \cdot I^T) + \alpha I_{identity})^{-1} \cdot (C \cdot I^T)$$

Using this system notation, the weightage vector W is calculated by solving the matrix using Penrose-Moore Pseudo Inverse and SVD method. A regularization factor (alpha, ridge) is introduced to discourage overfitting of solution.

Step 4

Identifying priority combinations

The weightage vector W defines the priority of each drug or each combination that enables the cohort genomics to attain the expected end-point. The maxima of the vector entry corresponds to the ideal solution of the ideal combination in this case of cohort X context

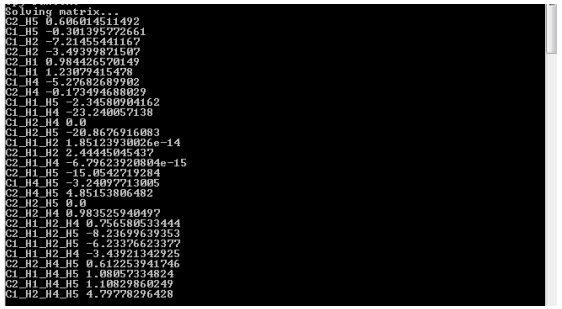
$$T = index(max(w))$$

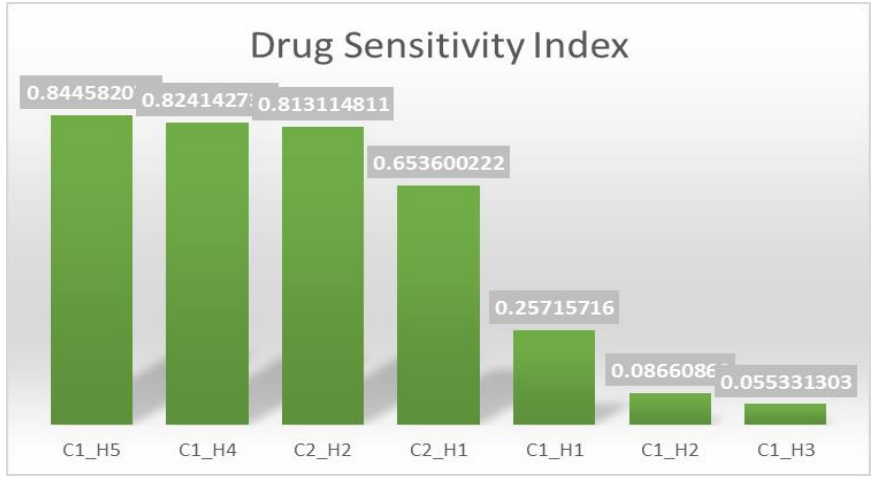
$$Combination^{*} = D[T]$$

VISUALIZING RESULTS

Visualizing Drug Combination Priority Ranking

Solver





Visualizing n-Dimensional Dose Response Curves

Solver